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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/735,916	GOETSCH ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-54* is/are pending in the application.

4a) Of the above claim(s) *18-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17 and 22-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 October 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/8/04; 4/6/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-54 are pending.

2. Applicant's election with traverse of Group 1, Claims 1-17, 22-30 and 43-54 drawn to an isolated antibody, or one of its functional fragments that binds human insulin-like growth factor T receptor and inhibits the natural attachment of its ligand IGFI and /or lGF2 and/or capable of specific the tyrosine kinase activity of said receptor, a hybridoma producing said antibody, a process of producing said antibody, a composition comprising said antibody or functional fragments thereof and a pharmaceutically acceptable carrier, a method for the preparation of a medicament using said antibody and a kit comprising said antibody, filed 12/2/05, is acknowledged.

The traversal is on the grounds that the presently claimed subject matter clearly exhibits unity of invention. With regard to a common utility, as well as a substantial structural feature, the compounds of the present claims associate with antibodies that bind human insulin-like growth factor T receptor and inhibit the natural attachment of its ligand IGF1 and/or IGF2 and/or capable of specific the tyrosine kinase activity of said receptor (e.g., claims 1-17, 22-30, and 43-54, in Group 1) and compositions comprising such antibodies (e.g., claims 31-44, in Groups IV-VII). The Examiner has indicated that claim 30 is a linking claim and will be examined along with Groups IV-VII if any one of said Groups is elected (page 3, final paragraph). As Group I includes claim 30, Applicants respectfully submit that joinder of Groups I and IV-VII is proper, that the compounds of the present claims clearly evidence unity of invention, and there would be no undue burden in searching. Regardless of whether the alleged seven inventions are independent or distinct, Applicants respectfully assert that the Examiner need not have restricted the application. MPEP § 803 requires that " if the search and examination of an entire application can be made without serious burden, the Examiner must examine it on the merits, even though it includes claims to independent or distinct inventions." Therefore, it is not mandatory to make a restriction requirement in all situations where it would be deemed proper."

This is not found persuasive because of the reasons set forth in the restriction mailed 11/2/05. As is well known in the art, polynucleotides such as claimed by Applicant are transcribed into RNA and the RNA is translated into protein. Thus polynucleotides encode proteins. Antibodies are proteins that bind to other proteins. The two types of molecules

therefore have different functions - the encoding of protein versus binding to other proteins, different modes of operation - transcription and translation versus protein-protein interactions - and different effects - production of protein versus interacting with another protein. Transgenic animal expresses a particular gene of interested. Thus, as was stated in the previous office action, they differ structurally and functionally and cannot be used together or interchangeably. Reasons as to why the other groups are distinct are also provided in the previous office action. A product is distinct from a process of use if it has other uses. Methods are different if they have different method steps, goals, or outcome measures. Further, a prior art search also requires a literature search. It is a burden to search more than one invention. With respect to the argument that the search and examination of all groups would not entail a "serious burden", the separate classification of the different groups provides prima facie evidence of such a burden; see MPEP § 803. Furthermore, antibodies, polynucleotides, and transgenic animal represent different inventions and require different, non-contiguous searches, as evidenced by their different classification. They require separate searches of separate databases. A search of polynucleotide databases does not reveal information about the protein sequence or the transgenic animal, nor does a search of polypeptide databases reveal information about polynucleotides and transgenic animal. The search for methods of use is separate because it requires additional considerations as to the methodology itself. Thus to consider all of these groups would constitute an undue burden because each requires considerations that are separate from each of the others.

It is agreed, however, that Groups 1 and 4-7 are hereby rejoined. Therefore, the requirement of Group 1 and Groups 2-3 is still deemed proper and is therefore made FINAL.

3. Claims 18-21 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 1-17 and 22-54 drawn to an isolated antibody, or one of its functional fragments that binds human insulin-like growth factor I receptor alone or in combination with a second compound wherein the second compound is an anti-EGF'R antibodies or functional fragment thereof or a cytotoxic or cytostatic agent, or tyrosine kinase activity inhibitor, or another antibody that directed against the extracellular domain of the HER2/neu receptor, a hybridoma producing the human insulin-like growth factor I receptor, a process of producing antibody that binds specifically human insulin-like growth factor I receptor, a composition comprising said antibody

or functional fragments thereof and a pharmaceutically acceptable carrier, a method for the preparation of a medicament using said antibody and a kit comprising said antibody, are being acted upon in this Office Action.

5. Claim 1 is objected to because of typographical error "human insulin-like growth factor **T** receptor" should have been "human insulin-like growth factor **I** receptor".

6. Claims 1-7, 10-17, 22-24, 29-30, and 42-43 are objected to because "one of its functional fragments" should have been "a binding fragment thereof".

7. Claim 32 is objected to because "anti-EGFR antibodies, or their functional fragments" should have been "an anti-EGFR antibody or a binding fragment thereof". Appropriate correction is required.

8. The drawings, filed 10/8/04, are not approved under 37 CFR 1.84(l) because Figure 42A is too dark and some of the bands are not legible. The numbers in x-axis of Figure 30 are overlapped and out of place. The numbering "J0, J10, ... J50" in the x-axis of Figure 31 appears to have the extract "J". Appropriate action is required.

9. The international search report on PTO 1449, filed 10/8/04 has been considered but crossed out because the search report is inappropriate to be printed on an issued patent.

10. The disclosure is objected to because of the following informalities: (1) the arrangement and layout of the specification does not comply with 37 CFR 1.77(b). (2) "**L**amoxifen" on page 82, line 10 is misspelled. It should have been "**t**amoxifen". (3) Incorporation of subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See MPEP 608.01(p), paragraph I regarding incorporation by reference. Therefore the embedded hyperlinks and/or other forms of browser-executable code disclosed on page 8, lines 13-14 and page 95, line 13-14 of the instant specification are impermissible and require deletion. Where the hyperlinks and/or other forms of browser-executable codes are part of applicant's invention and are necessary to be included in the patent application in order to comply with the requirements of 35 U.S.C. 112, first paragraph, and

applicant does not intend to have these hyperlinks be active links, then this objection will be withdrawn and the Office will disable these hyperlinks when preparing the patent text to be loaded onto the PTO web database. Appropriate correction is required.

11. The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT
(e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC (See 37 CFR 1.52(e)(5) and MPEP 608.05. Computer program listings (37 CFR 1.96(c)), "Sequence Listings" (37 CFR 1.821(c)), and tables having more than 50 pages of text are permitted to be submitted on compact discs.) or
REFERENCE TO A "MICROFICHE APPENDIX" (See MPEP § 608.05(a). "Microfiche Appendices" were accepted by the Office until March 1, 2001.)
(f) BACKGROUND OF THE INVENTION.
(1) Field of the Invention.
(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(g) BRIEF SUMMARY OF THE INVENTION.
(h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(i) DETAILED DESCRIPTION OF THE INVENTION.
(j) CLAIM OR CLAIMS (commencing on a separate sheet).
(k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

12. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 1-17 and 22-54 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is apparent that the hybridoma deposited at the CNCM under the number I-2717 as recited in claims 9 and 10 are required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification.

If it is not so obtainable or available, a deposit of said hybridoma cell lines may satisfy the enablement requirements of 35 U.S.C. 112, first paragraph. See 37 CFR 1.801-1.809.

If the deposit has been made under the terms of the Budapest Treaty, an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the hybridoma secreting said antibody have been deposited under the Budapest Treaty and that the hybridoma will be irrevocably and without restriction or condition released to the public upon the issuance of a patent would satisfy the deposit requirement made herein. See 37 CFR 1.808.

If the deposit has not been made under the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature must be made, stating that the deposit has been made at an acceptable depository and that the criteria set forth in 37 CFR 1.801-1.809, have been met.

Amendment of the specification to recite the date of deposit for hybridoma under the number I-2717 and the complete name and address of the depository is required.

Further, the specification does not teach how to make and use (1) any isolated antibody or any functional fragments of any antibody capable of binding to the human "insulin-like growth factor I receptor (IGF-IR)" comprising any *combination* of any light chain comprising at least any one, or two complementary determining region (CDR)"selected from the CDRs of sequence of

SEQ ID NO: 2, 4 or 6 or at least any one CDR whose sequence has "at least 80% identity to SEQ ID NO: 2, 4 or 6 and heavy chain comprising any combination of at least any one or two CDR from the CDRs of sequence SEQ ID NO: 8, 10, and 12 or at least any one CDR whose sequence has "at least 80% identity" after optimum alignment with the sequence of SEQ ID NO: 8, 10 and 12 as set forth in claims 1-7 and 29, (2) any murine hybridoma capable of secreting any antibody mentioned above, (3) any antibody or its functional fragments capable of binding to the human "insulin-like growth factor I receptor (IGF-IR)" wherein said antibody comprises a light chain of sequence comprising the amino acid sequence SEQ ID NO: 54 **or** in that it comprises a heavy chain of sequence comprising the amino acid sequence SEQ ID NO: 69 (claim 11), (4) any antibody or its functional fragments capable of binding to the human insulin-like growth factor I receptor (IGF-IR) wherein said antibody comprises any light chain sequence having "at least 80% identity" after optimum alignment with the sequence of SEQ ID NO: 54 **or**/and any heavy chain sequence comprising the amino acid sequence comprising the amino acid sequence SEQ ID NO: 69, or any sequence having "at least 80% identity" after optimum alignment with the sequence SEQ ID NO: 69 (claim 11), (5) any chimeric antibody or its functional fragments as set forth in claims 12-14, (6) any humanized antibody as set forth in claims 15-17, (7) a process for production of any antibody or its functional fragment as set forth in claim 22 and any antibody or fragment thereof produced by the process as set forth in claim 23, (8) any bispecific antibody as set forth in claims 24-28, (9) any composition comprising any compound consisting of any isolated antibody or any functional fragments of any antibody capable of binding to the human insulin-like growth factor I receptor (IGF-IR) comprising any *combination* of any light chain comprising at least any one, or two complementary determining region (CDR)" selected from the CDRs of sequence of SEQ ID NO: 2, 4 *or* 6 or at least any one CDR whose sequence has "at least 80% identity to SEQ ID NO: 2, 4 or 6 and heavy chain comprising any combination of at least any one, or two CDR from the CDRs of sequence SEQ ID NO: 8, 10, and 12 or at least any one CDR whose sequence has "at least 80% identity" after optimum alignment with the sequence of SEQ ID NO: 8, 10 and 12 (Claims 30 and 44), (10) any composition mentioned above further comprising any "second compound" (claim 31), any anti-EGFR antibodies or functional fragment thereof (claims 32-35), any cytotoxic or cytostatic agent or "derived natural agents" (claims 36-40), any antibody directed to the extracellular domain of the HER2/neu receptor (claim 41-42), (11) any composition comprising any conjugated antibodies as set forth in claim 43, (12) a method of preparing any medicament for the "prevention" of any illness such as any endometrial

cancer, colon cancer, psoriasis connected with any overexpression and/or abnormal activation of the IGF-R and/or EGFR receptor comprising using any antibody mentioned above (claims 45-51 and 54), (13) any in vitro diagnosis of illnesses using any isolated antibody or any functional fragments of any antibody capable of binding to the human insulin-like growth factor I receptor (IGF-IR) comprising any *combination* of any light chain comprising at least any one, or two complementary determining region (CDR)"selected from the CDRs of sequence of SEQ ID NO: 2, 4 or 6 or at least any one CDR whose sequence has "at least 80% identity" to SEQ ID NO: 2, 4 or 6 and heavy chain comprising any *combination* of at least any one, or two CDR from the CDRs of sequence SEQ ID NO: 8, 10, and 12 or at least any one CDR whose sequence has "at least 80% identity" after optimum alignment with the sequence of SEQ ID NO: 8, 10 and 12, optionally labeled (claim 52) and (14) any kit comprising any isolated antibody or any functional fragments of any antibody capable of binding to the human "insulin-like growth factor I receptor (IGF-IR)" comprising any *combination* of any light chain comprising at least any one, or two complementary determining region (CDR)"selected from the CDRs of sequence of SEQ ID NO: 2, 4 or 6 or at least any one CDR whose sequence has "at least 80% identity" to SEQ ID NO: 2, 4 or 6 and heavy chain comprising any combination of at least any one, or two CDR from the CDRs of sequence SEQ ID NO: 8, 10, and 12 or at least any one CDR whose sequence has "at least 80% identity" after optimum alignment with the sequence of SEQ ID NO: 8, 10 and 12 as set forth in claim 53.

The specification discloses only one isolated monoclonal antibody (7C10) or a binding fragment thereof that binds specifically to human insulin-like growth factor I receptor (IGF-IR) wherein the antibody comprises a light chain amino acid sequence of SEQ ID NO: 54 and a heavy chain amino acid sequence of SEQ IDNO: 69 and wherein the antibody inhibits the binding of its ligand IGF-1 and/or IGF2 from binding to said IGF-IR receptor. The isolated antibody or a binding fragment thereof mentioned above is capable of inhibiting tyrosine phosphorylation of IGF-IR or IRS-1. The specification further discloses humanized antibodies (1H7 and 7H2HM) or a binding fragment thereof that binds specifically to human insulin-like growth factor I receptor (IGF-IR) wherein the antibody comprises a light chain amino acid sequence SEQ ID NO: 65 *and* a heavy chain amino acid sequence selected from the group consisting of SEQ IDNO: 79 and 83. The specification also discloses a chimeric antibody or a binding fragment thereof that binds specifically to human insulin-like growth factor I receptor (IGF-IR) wherein the antibody comprises *three* complentarity determining region (CDR) from the

light chain consisting of the amino acid sequence of SEQ ID NO: 2, 4 and 6 and *three* complentarity determining region (CDR) from the heavy chain consisting of the amino acid sequence of SEQ ID NO: 8, 10 and 12. The specification discloses administering monoclonal antibody (7C10) or a chimeric or humanized antibody thereof that binds specifically to human insulin-like growth factor I receptor (IGF-IR) mentioned above inhibits the IGF1-induced growth of the MCF-7 (breast) tumor (page 85) and non-small cell tumor of the lung A549 (page 87). The specification discloses co-administration of monoclonal antibody (7C10) that binds specifically to human insulin-like growth factor I receptor (IGF-IR) and anti-EGFR 225 antibody or navelbine inhibits the growth of tumor A549 and increases the mice survival (page 125).

The specification does not teach how to make any and all antibody and functional fragments of any antibody mentioned above, much less for treating or "preventing" any "illness" as broadly as claimed. There is insufficient guidance as to the binding specificity of any and all antibody having any combination and subcombination of at least one or two CDR from any heavy and light chains. There is insufficient guidance as to which combination of heavy and light chain or which combination of CDR1, CDR2 or CDR3 from which heavy chain and/or which combination of CDR1, CDR2 or CDR3 from which light chain that the undisclosed antibody would maintain the same binding specificity as the claimed antibody that binds specifically to human insulin-like growth factor I receptor (IGF-IR).

Janeway et al teach that the association of different heavy and light chain variable regions from the binding site (See page 3:21, last paragraph, in particular). However, the function of an antibody molecule is dependent on its three dimensional structure, which in turn is dependent on its primary amino acid sequence. Changing the amino acid sequence of an antibody may adversely affect its activity. Likewise, fragments of the antibody may not retain the appropriate three dimensional structure necessary to foster binding activity. Moreover, a change in the DNA sequence coding for the antibody may affect the ability of the cell containing the DNA sequence to express, secrete or assemble the antibody. The exact residues comprising CDRs are difficult to define and do not necessarily correspond to all the residues in the hypervariable regions, as defined by the Kabat numbering system. There are also critical framework residues which are important in positioning the CDRs for interaction with antigen or which are involved in interactions between the heavy and light chains. Therefore, it is not clear that any combination of CDR regions from heavy and/or light chains will have the asserted utility of binding to human insulin-like growth factor I receptor (IGF-IR), without further guidance from the specification.

With regard to "80% sequence identity", the specification does not teach any assays that is useful for screening variants and is predictive of success *in vivo* in treating and/or "preventing" any and all illness. It is known in the art that even a single amino acid change in the CDRs of an antibody can lead to unpredictable changes in the binding specificity and biological activity of the antibody in vivo. The actual biological activity and the functional fragments per se in treating all diseases such as psoriasis remain to be demonstrated. With regard to "functional fragments", there is not a single fragment from the smallest to the largest fragment shows any biological effect in vivo for treating or preventing any illness such as cancer.

With regard to "at least 80% identity to SEQ ID NO: 2, 4 or 6" *or* "at least one CDR whose sequence has "at least 80% identity with sequence of SEQ ID NO: 8, 10 and 12", a sequence identity of 80% means at there is at least 20% differences in the CDRs of light and heavy chains. There is insufficient guidance as to which amino acids within the light chain CDRs of SEQ ID NO: 2, 4 or 6 to be substituted for which amino acids, deleted, added and/or combination thereof such that the modified antibody still binds specifically to human IGF-IR. Likewise, there is insufficient guidance as to which amino acids within the heavy chain CDRs of SEQ ID NO: 8, 10 and 12 to be substituted for which amino acids, deleted, added and/or combination thereof such that the modified antibody still binds specifically to human IGF-IR. The same reasoning applies to claim 2. With regard to the term "or", the CDRs from the other chain are not enabled without the amino acid sequence. With regard to the term "at least one or two", the rest of the CDRs in the light chain and/or heavy chains are not enable without the amino acid sequence.

With regard claim 6, it is not clear which "manner" the claimed antibody does not attached significantly.

With regard to claim 11, "having at least 80% identity" means there is at least 20% difference in SEQ ID NO: 54 "**or**/and" .... SEQ ID NO: 69. There is inadequate guidance about which amino acids within the SEQ ID NO: 54 and SEQ ID NO: 69 to be modified by substitution, deletion, addition and/or combination thereof such that the modified light chain or heavy chain in the claimed antibody still binds specifically to the human insulin like growth factor I receptor (IGF-IR). Let alone the antibody can treat or prevent any illness such as cancer. In addition to the lack of guidance as to the "at least 80% identity" in the light chain sequence, the heavy chain sequence of the claimed antibody is not enable without the amino acid sequence because of the term "or". The same reasoning applies to claim 16.

With regard to "second motif" in claim 25, there is inadequate guidance about the "second motif" that inhibits the attachment of the EGF to the human epidermal growth factor receptor (EGFR) and/or inhibiting the tyrosine kinase activity of said EGFR receptor without the amino acid sequence.

With regard to "second compound" in claim 31, there is a lack of guidance about the structure associated with function of any and all "second compound" without the amino acid sequence or chemical structure.

Given the unlimited number of antibody and fragments thereof, there is insufficient in vivo working example showing that any undisclosed antibody comprising any one CDR whose sequence is merely 80% sequence identity with SEQ ID NO: 2, 4, 6, 8, 10 or 12 still binds specifically to human insulin-like growth factor I receptor (IGF-IR), let alone inhibits the natural attachment of IGF1 and/or IGF2, in turn, would be effective for treating and/or preventing all illnesses. Further, the specification does not adequately teach how to effectively *prevent* any cancer or psoriasis and reach any therapeutic endpoint in humans by administering any undisclosed antibody or binding fragment thereof. The specification as filed does not adequate teaches which illness or illnesses is/are associated overexpression of IGF-IR and EGFR receptor alone? Which illness or illnesses is/are associated with underexpression of IGF-IR and EGFR receptor? Which illness or illnesses is/are associated underexpression of IGF-IR or EGFR receptor alone? How does one diagnosis overexpression or underexpression of the *EGFR* receptor in the claimed method using the antibody in claim 1 that binds specifically to human IGF-IRI?

Gura et al teach the shortcomings of potential anti-cancer agents including extrapolating from in vitro protocols, the problems of drug testing for cancer is that the model system are not predictive at all.

Given the lack of guidance as to the binding specificity of other antibody other than the specific monoclonal antibody (7C10) and humanized version thereof, it is unpredictable which undisclosed antibody is effective as a composition for treating and/or preventing any and all cancer. Since the binding specificity of the antibody and functional fragments thereof are not enabled, it follows that any composition or kit comprising the undisclosed antibody are not enabled. It also follows that any compositions comprising the undisclosed antibody in combination with any undisclosed "second compound" (claim 31), any anti-EGFR antibodies or functional fragments thereof (claims 32-35), any cytotoxic or cytostatic agent or "derived natural

agents" (claims 36-40), any antibody directed to the extracellular domain of the HER2/neu receptor (claim 41-42) are not enabled. It also follows that any conjugated antibody comprising any undisclosed antibody or functional fragments thereof are not enabled. Given the lack of guidance as to the binding specificity of any antibody and the lack of guidance as to the structure of any immunogen, it also follows that the method of making any undisclosed antibody with the intended to treat, to prevent or to diagnose any and all illnesses are not enabled (claims 45-52 and 54).

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

15. Claims 1-17 and 22-54 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) any isolated antibody or any functional fragments of any antibody capable of binding to the human "insulin-like growth factor I receptor (IGF-IR)" comprising any *combination* of any light chain comprising at least any one, or two complementary determining region (CDR)"selected from the CDRs of sequence of SEQ ID NO: 2, 4 or 6 or at least any one CDR whose sequence has "at least 80% identity to SEQ ID NO: 2, 4 or 6 and heavy chain comprising any combination of at least any one or two CDR from the CDRs of sequence SEQ ID NO: 8, 10, and 12 or at least any one CDR whose sequence has "at least 80% identity" after optimum alignment with the sequence of SEQ ID NO: 8, 10 and 12 as set forth in claims 1-7 and 29, (2) any murine hybridoma capable of secreting any antibody mentioned above, (3) any antibody or its functional fragments capable of binding to the human "insulin-like growth factor I receptor (IGF-IR)" wherein said antibody

comprises a light chain of sequence comprising the amino acid sequence SEQ ID NO: 54 **or** in that it comprises a heavy chain of sequence comprising the amino acid sequence SEQ ID NO: 69 (claim 11), (4) any antibody or its functional fragments capable of binding to the human insulin-like growth factor I receptor (IGF-IR) wherein said antibody comprises any light chain sequence having "at least 80% identity" after optimum alignment with the sequence of SEQ ID NO: 54 **or**/and any heavy chain sequence comprising the amino acid sequence comprising the amino acid sequence SEQ ID NO: 69, or any sequence having "at least 80% identity" after optimum alignment with the sequence SEQ ID NO: 69 (claim 11), (5) any chimeric antibody or its functional fragments as set forth in claims 12-14, (6) any humanized antibody as set forth in claims 15-17, (7) a process for production of any antibody or its functional fragment as set forth in claim 22 and any antibody or fragment thereof produced by the process as set forth in claim 23, (8) any bispecific antibody as set forth in claims 24-28, (9) any composition comprising any compound consisting of any isolated antibody or any functional fragments of any antibody capable of binding to the human insulin-like growth factor I receptor (IGF-IR) comprising any *combination* of any light chain comprising at least any one, or two complementary determining region (CDR)" selected from the CDRs of sequence of SEQ ID NO: 2, 4 *or* 6 or at least any one CDR whose sequence has "at least 80% identity to SEQ ID NO: 2, 4 or 6 and heavy chain comprising any combination of at least any one, or two CDR from the CDRs of sequence SEQ ID NO: 8, 10, and 12 or at least any one CDR whose sequence has "at least 80% identity" after optimum alignment with the sequence of SEQ ID NO: 8, 10 and 12 (Claims 30 and 44), (10) any composition mentioned above further comprising any "second compound" (claim 31), any anti-EGFR antibodies or functional fragment thereof (claims 32-35), any cytotoxic or cytostatic agent or "derived natural agents" (claims 36-40), any antibody directed to the extracellular domain of the HER2/neu receptor (claim 41-42), (11) any composition comprising any conjugated antibodies as set forth in claim 43, (12) a method of preparing any medicament for the "prevention" of any illness such as any endometrial cancer, colon cancer, psoriasis connected with any overexpression and/or abnormal activation of the IGF-R and/or EGFR receptor comprising using any antibody mentioned above (claims 45-51 and 54), (13) any in vitro diagnosis of illnesses using any isolated antibody or any functional fragments of any antibody capable of binding to the human insulin-like growth factor I receptor (IGF-IR) comprising any *combination* of any light chain comprising at least any one, or two complementary determining region (CDR)"selected from the CDRs of sequence of SEQ ID NO: 2, 4 or 6 or at least any one

CDR whose sequence has "at least 80% identity" to SEQ ID NO: 2, 4 or 6 and heavy chain comprising any *combination* of at least any one, or two CDR from the CDRs of sequence SEQ ID NO: 8, 10, and 12 or at least any one CDR whose sequence has "at least 80% identity" after optimum alignment with the sequence of SEQ ID NO: 8, 10 and 12, optionally labeled (claim 52) and (14) any kit comprising any isolated antibody or any functional fragments of any antibody capable of binding to the human "insulin-like growth factor I receptor (IGF-IR)" comprising any *combination* of any light chain comprising at least any one, or two complementary determining region (CDR)"selected from the CDRs of sequence of SEQ ID NO: 2, 4 or 6 or at least any one CDR whose sequence has "at least 80% identity" to SEQ ID NO: 2, 4 or 6 and heavy chain comprising any combination of at least any one, or two CDR from the CDRs of sequence SEQ ID NO: 8, 10, and 12 or at least any one CDR whose sequence has "at least 80% identity" after optimum alignment with the sequence of SEQ ID NO: 8, 10 and 12 as set forth in claim 53.

The specification discloses only one isolated monoclonal antibody (7C10) or a binding fragment thereof that binds specifically to human insulin-like growth factor I receptor (IGF-IR) wherein the antibody comprises a light chain amino acid sequence of SEQ ID NO: 54 and a heavy chain amino acid sequence of SEQ IDNO: 69 and wherein the antibody inhibits the binding of its ligand IGF-1 and/or IGF2 from binding to said IGF-IR receptor. The isolated antibody or a binding fragment thereof mentioned above is capable of inhibiting tyrosine phosphorylation of IGF-IR or IRS-1. The specification further discloses humanized antibodies (1H7 and 7H2HM) or a binding fragment thereof that binds specifically to human insulin-like growth factor I receptor (IGF-IR) wherein the antibody comprises a light chain amino acid sequence SEQ ID NO: 65 *and* a heavy chain amino acid sequence selected from the group consisting of SEQ IDNO: 79 and 83. The specification also discloses a chimeric antibody or a binding fragment thereof that binds specifically to human insulin-like growth factor I receptor (IGF-IR) wherein the antibody comprises *three* complementarity determining region (CDR) from the light chain consisting of the amino acid sequence of SEQ ID NO: 2, 4 and 6 and *three* complementarity determining region (CDR) from the heavy chain consisting of the amino acid sequence of SEQ ID NO: 8, 10 and 12. The specification discloses administering monoclonal antibody (7C10) or a chimeric or humanized antibody thereof that binds specifically to human insulin-like growth factor I receptor (IGF-IR) mentioned above inhibits the IGF1-induced growth of the MCF-7 (breast) tumor (page 85) and non-small cell tumor of the lung A549 (page 87). The specification discloses co-administration of monoclonal antibody (7C10) that binds specifically to

human insulin-like growth factor I receptor (IGF-IR) and anti-EGFR 225 antibody or navelbine inhibits the growth of tumor A549 and increases the mice survival (page 125).

With the exception of the specific monoclonal antibody and humanized antibodies mentioned above, there is insufficient written description about the structure such as the CDRs of light chain and CDRs of heavy chains associated with the binding specificity of any and all antibody and functional fragments thereof. The term "at least one CDR selected from the CDRs of sequence SEQ ID NO: 2, 4 **or** 6" in claim 1 does not adequate describe the other two or three CDRs of light chain in the claimed antibody. In addition, there is inadequate written description about the structure of the other two or three CDRs from the heavy chain in the claimed antibody without the amino acid sequence. The same reasoning applies to claims 3-5.

With regard to "at least 80% identity to SEQ ID NO: 2, 4 or 6" *or* "at least one CDR whose sequence has "at least 80% identity with sequence of SEQ ID NO: 8, 10 and 12", a sequence identity of 80% means at there is at least 20% differences in the CDRs of light and heavy chains. There is inadequate written description about which amino acids within the light chain CDRs of SEQ ID NO: 2, 4 or 6 to be substituted for which amino acids, deleted, added and/or combination thereof such that the modified antibody still binds specifically to human IGF-IR. Likewise, there is inadequate written description about which amino acids within the heavy chain CDRs of SEQ ID NO: 8, 10 and 12 to be substituted for which amino acids, deleted, added and/or combination thereof such that the modified antibody still binds specifically to human IGF-IR. The same reasoning applies to claim 2.

With regard to claim 6, it is not clear which "manner" the claimed antibody does not attached significantly.

With regard to claim 11, "having at least 80% identity" means there is at least 20% difference in SEQ ID NO: 54 "**or**/and" .... SEQ ID NO: 69. There is inadequate written description about which amino acids within the SEQ ID NO: 54 and SEQ ID NO: 69 to be modified by substitution, deletion, addition and/or combination thereof such that the modified light chain in the claimed antibody still binds specifically to the human IGF-IR. In addition to the lack of a written description about the "at least 80% identity" in the light chain sequence, the heavy chain sequence of the claimed antibody is not adequate describe because of the term "or". The same reasoning applies to claim 16.

With regard to "second motif" in claim 25, there is inadequate written description about the "second motif" that inhibits the attachment of the EGF to the human epidermal growth factor

receptor (EGFR) and/or inhibiting the tyrosine kinase activity of said EGFR receptor without the amino acid sequence.

With regard to "second compound" in claim 31, there is inadequate written description about the structure associated with function of any and all "second compound" without the amino acid sequence or chemical structure. Since the binding specificity of the antibody and functional fragments thereof are not adequately described, it follows that any composition or kit comprising any undisclosed antibody are not adequately described. It also follows that any compositions comprising the undisclosed antibody in combination with any undisclosed "second compound" (claim 31), any anti-EGFR antibodies or functional fragments thereof (claims 32-35), any cytotoxic or cytostatic agent or "derived natural agents" (claims 36-40), any antibody directed to the extracellular domain of the HER2/neu receptor (claim 41-42) are not adequately described. It also follows that any conjugated antibody comprising any undisclosed antibody or any functional fragments thereof for targeting any biological compound are not adequately described. Given the lack of a written description about the structure of the CDRs of any and all antibodies, it also follows that the method of making any undisclosed antibody with the intended to treat, particular to prevent or to diagnose any and all illnesses are not adequately described (claims 45-52 and 54).

The specification discloses only *one* monoclonal antibody 7C10 that binds specifically to human insulin-like growth factor I receptor (IGF-IR) and a humanized or chimeric antibody thereof for inhibiting tumor cell proliferation wherein the tumor cell expressing the human IGF-IR, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of antibody to human insulin-like growth factor I receptor (IGF-IR), anti-EGFR antibodies, "second compound", "second motif", "agent interacting with DNA" to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

16. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

17. Claims 1-8, 11-17 and 22-54 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is noted that the claims are so poorly written and appear to be a translation from a foreign document. Please amend *all* claims to conform to US practice.

The term "if necessary" in claim 1 is ambiguous and indefinite because one of ordinary skill in the art cannot appraise the metes and bound of the claimed invention. It is suggested that claim 1 be amended to recite "An isolated antibody or a binding fragment thereof that binds specifically to the human insulin-like growth factor receptor (IGF-IR) wherein the antibody comprising light chain complementarity determining region (CDRs) of SEQ ID NO: 2, 4 and 6 and heavy chain complementarity determining region (CDRs) of SEQ ID NO: 8, 10 and 10 wherein the binding of the antibody or fragment thereof to said IGF-IR inhibits the natural attachment of its ligand IGF1 and/or IGF2 to said IGF-IR and wherein the binding of the antibody or fragment thereof to said IGF-IR inhibits the tyrosine kinase phosphorylation of said IGF-IR", for example.

The "...which does not attach in a *significant manner* to the human insulin receptor IR" in claim 6 is ambiguous and indefinite. It is not clear which "manner" the claimed antibody does not attached significantly. One of ordinary skill in the art cannot appraise the metes and bounds of the claimed invention.

The "...or any fragment whose half-life would have been increased such as pegylated fragments" in claims 7 and 34 has no antecedent basis in base claim 1 and claim 32, respectively. The antibody fragments in claims 1 and 32 are not "pegylated fragments".

The term "having" or "has" in claims 2, 3, 4, 5, 11, 16 is ambiguous and indefinite. If the sequence is intended to be open, it is suggested that the term "comprising" be used. If the sequence is intended to be close, it is suggested that the term "consisting of" be used.

With regard to claim 8, a hybridoma does not secrete antibody fragments as set forth in claim 1. One of ordinary skill in the art cannot appraise the metes and bounds of the claimed invention.

The "moreover comprises" in claim 12 is ambiguous and indefinite because by definition, a chimeric antibody comprises the light chain and heavy chain constant regions derived from an antibody of a species heterologous to the mouse monoclonal antibody in claim 11. It is not clear if the term "moreover comprises" to mean further comprises light chain and heavy chain constant

regions derived from an antibody of a species heterologous to the mouse in addition to the basic definition. One of ordinary skill in the art cannot appraise the metes and bounds of the claimed invention.

The "...culture of a cell" in claim 22 is ambiguous and indefinite because culturing any cell in a medium and appropriate culture conditions does not produce the claimed antibody or its functional fragments. One of ordinary skill in the art cannot appraise the metes and bounds of the claimed invention. In order to produce the antibody as claimed, the cell must be transfected with a polynucleotide encoding the claimed antibody or its binding fragment thereof.

The "antibody or one of its functional fragments, ...**moreover**, capable of attaching specifically to the human epidermal growth factor receptor...EGFR" in claim 24 is ambiguous and indefinite because it is not clear if the antibody in claim 24 that binds to human insulin-like growth factor I receptor (IGF-IR) also cross-react with human epidermal growth factor receptor...EGFR or if it is a bispecific antibody that binds to both IGF-IR and EGFR.

The singular "...said anti-EGFR *antibody* is selected from monoclonal, chimeric, or humanized anti-EGFR *antibodies* or their functional fragments." in claim 33 does not correlate with the plural antibodies in claim 33. It is suggested that claim 33 be amended to recite the composition as claimed in claim 32 wherein said anti-EGFR antibody is a monoclonal, a chimeric, a humanized anti-EGFR antibody or a binding fragment thereof.

The "said anti-EGFR **antibody**" in claim 33 has no antecedent basis in base claim 32. Base claim 32 recites "...anti-EGFR **antibodies**, or their functional fragments...EGFR". It is suggested that claim 32 be amended to recite the composition as claimed in claim 31 wherein the second antibody is an anti-EGFR antibody or a binding fragment thereof capable of inhibiting by competition the attachment of the epidermal growth factor (EGF) to the epidermal growth factor receptor (EGFR).

The "second motif" in claims 25 and 27 is ambiguous and indefinite. Is the "second motif" an antibody or a peptide? One of ordinary skill in the art cannot appraise the metes and bound of the claimed invention.

The composition as written in claim 30 is a compound, not a composition. At minimum, a composition comprising the antibody or the binding fragment thereof as claimed in claim 1 and a pharmaceutical acceptable carrier.

The "like pegylated fragments" in claims 34 is ambiguous and indefinite. What is meant by "like" ? One of ordinary skill in the art cannot appraise the metes and bound of the claimed invention.

The "*or else* any agent capable of being used in chemotherapy" in claim 37 is indefinite and ambiguous. One of ordinary skill in the art cannot appraise the metes and bound of the claimed composition.

The "one of the elements" in claim 38 is indefinite and ambiguous. One of ordinary skill in the art cannot appraise the metes and bound of the claimed composition.

The "derived natural agents" and "or else" in claim 40 are indefinite and ambiguous. One of ordinary skill in the art cannot appraise the metes and bound of the claimed composition.

The "antibody compound" in claim 41 is indefinite and ambiguous. Is the antibody compound an antibody or something conjugated to the antibody that binds to the extracellular domain of the HER2/neu receptor? One of ordinary skill in the art cannot appraise the metes and bound of the claimed composition.

The "said antibodies" in claim 43 has no antecedent basis in base claim 30. Base claim 30 recites a composition comprising a compound consisting of an *antibody*.

"the *administration* of medicament does not induce or only slightly induces *secondary effects* connected with inhibition of the insulin receptor IR" in claim 46 has no antecedent basis in base claim 45. Base claim 45 recite a method of *preparing* a medicament, now the dependent claim 46 becomes a method of treating by administering the medicament instead of preparing the medicament. Further, it is not clear which "secondary effect" connected with inhibition of the insulin receptor IR is part of the claimed invention.

The "preferably" in claims 47 and 48 is indefinite and ambiguous. One of ordinary skill in the art cannot appraise the metes and bound of the claimed composition.

The "...method of in vitro diagnosis of illnesses....it being possible for said antibody to be, optionally, labeled" in claim 52 is indefinite and ambiguous. What is meant by "it"? Further, which illness is associated with overexpression of IGF-IR *and* EGFR receptor? Which illness is associated overexpression of IGF-IR *or* EGFR receptor alone? Which illness is associated with underexpression of IGF-IR *and* EGFR receptor? Which illness is associated underexpression of IGF-IR *or* EGFR receptor alone? How does one diagnosis overexpression or underexpression of the *EGFR* receptor in the claimed method using the antibody in claim 1 that binds specifically to

human *IGF-IR*? These are two separate antibodies with different binding specificity. One of ordinary skill in the art cannot appraise the metes and bound of the claimed composition.

The "kit ...comprising an antibody or its functional fragments, as claimed in claim 1 ..." in claim 53 is ambiguous and indefinite. How is one going to diagnosis overexpression or underexpression of the *EGFR* receptor in the claimed method using the antibody that binds only to human IGF-IRI in claim 1 using the kit to carry out the method of diagnosis? How is the IGF-IR antibody forms immune complex with EGFR? Again, These are two separate antibodies with different binding specificity. One of ordinary skill in the art cannot appraise the metes and bound of the claimed kit. Further, "its functional fragments" should have been "a binding fragment thereof".

18. Claims 45-51 and 54 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01.

The omitted steps in claim 45 are: how to make and isolate the antibody for preparing the medicament.

The omitted steps in claim 54 are: how to make and isolate the antibody for preparing the medicament. Further, how to make and target a biological compound using the *unconjugated* antibody that binds to IGF-IR to a total different receptor such as EGFR receptor?

19. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

20. The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is

determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

21. Claims 1, 4, 6, 15, 22-24, 30, 44-52 and 54 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No. 5,891,996 (issued April 1999; PTO 892) as evidence by Rodeck et al (J Cell Biochem 35(4): 315-20, Dec 1987; PTO 892).

The '996 patent teaches various antibodies such as humanized, chimeric and monoclonal antibodies against human EGF receptor and a method of making the reference antibodies (see entire document, abstract, col. 5 through col. 9, in particular). As evidence by the teachings of Rodeck et al, Rodeck et al teach human EGF receptor is a human type I insulin-like growth factor (IGF) receptor (see abstract, in particular). The reference antibodies inherently also bind to the claimed human insulin-like growth factor I receptor and inhibit the natural ligand such as IGF1 and IGF2 from binding to its IGF-IR. This is because the reference monoclonal antibody mAb R3 having a light chain comprising at least one CDR that is 83.9% identical to the claimed SEQ ID NO: 6 (see reference SEQ ID NO: 31, in particular). The reference antibody inherently also binds (cross-reactive) to the claimed human insulin-like growth factor T receptor IGF-IR. Since the Patent Office does not have the facilities for examining and comparing the antibodies of the instant invention to those of the prior art, the burden is on applicant to show that the prior art antibody is different from the claimed antibody. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977). The reference inherently does not bind to human insulin receptor IR. The '996 patent further teaches a composition comprising the reference antibody and a pharmaceutical acceptable carrier for use in treating tumor and/or diagnosis of tumor (see col. 4, lines 4-12, in particular). The reference humanized antibody comprises a kappa light chain and a heavy chain of human IgG1 (see col. 3, lines 64-67, in particular) that contains the human framework segments FR1 to FR4 of human heavy and light chain (see col. 6, lines 30-40, in particular). The reference antibodies also bind to human epidermal growth factor receptor and inherently inhibit tyrosine kinase activity. The intended use in Claims 45-51 and 54 has no patentable weight because a product is a product, irrespective of its intended use. The '996 patent teaches a method of making or preparing the reference antibodies for treating tumor and/or diagnosis of tumor (see entire document, abstract, col. 5 through col. 9, col. 4, lines 4-12, in particular). Thus, the reference teachings anticipate the claimed invention.

22. Claims 1, 6-8, 11 and 22-23 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No. 5,935,821 (issued Aug 1999; PTO 892).

The '821 patent teaches monoclonal antibody comprising a light chain having a sequence such as SEQ ID NO: 66 that is 93.4% identical the claimed SEQ ID NO: 54, which is at least 80% identical to the claimed SEQ ID NO: 54 (see SEQ ID NO: 66 of the '821 patent, in particular). The term "or" in claims 1, and 11 does not require the antibody to have the other sequence from the light chain. The reference antibody inherently also binds (cross-reactive) to the claimed human insulin-like growth factor T receptor IGF-IR. Since the Patent Office does not have the facilities for examining and comparing the antibodies of the instant invention to those of the prior art, the burden is on applicant to show that the prior art antibody is different from the claimed antibody. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977). The '821 teaches a hybridoma under accession no. HB-11786 that is capable of secreting the reference antibody (see col. 13, lines 52-54, in particular). The '821 patent also teaches a method of making the reference antibody and antibody fragments such as scFv (see col. 13, lines 24 bridging col. 14, lines 1-56, col. 25, line 18-68, in particular), diabodies (see col. 25, line 57-58, in particular), Fab, F(ab')2, Fab' (see col. 8, lines 23-26, in particular). The reference antibody or its binding fragment thereof does not bind in a signifiant manner to the human insulin recpetor IR since it binds specifically to the paratope of antiobyd that binds to ganglioside GD2. Thus, the reference teachings anticipate the claimed invention.

23. Claims 1, 15 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No. 5,608,039 (issued March 4, 1997; PTO 892).

The '039 patent teaches an antibody such as humanized antibody and binding fragment thereof comprising a light chain sequence such as SEQ ID NO: 50 that has a 94.1% sequence identity with the claimed sequences of SEQ ID NO: 61 and SEQ ID NO: 65, which is at least 80% identical to the claimed SEQ ID NO: 61 and 65, for treating cancer (see reference SEQ ID NO: 50, in particular). The reference light chain is humanized (see col. 16, lines 15 through col. 17, in particular). The term "or" in claim 16 does not require the antibody to have the other sequence from the light chain. The reference antibody inherently also binds (cross-react) to human insulin-like growth factor T receptor IGF-IR given the high sequence identity. Since the Patent Office does not have the facilities for examining and comparing the antibodies of the instant invention to those of the prior art, the burden is on applicant to show that the prior art

antibody is different from the claimed antibody. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977). The reference humanized antibody inherently comprises FR1 to FR4 of human antibody and ligth and heavy chain. Thus, the reference teachings anticipate the claimed invention.

24. Claims 1, 8 and 11-16 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No. US Pat No. 6,068,841 (issued May 2000; PTO 892).

The '841 patent teaches a monoclonal antibody comprising a heavy chain sequence such as SEQ ID NO: 11 that has a 86.5% sequence identity with the claimed sequence of SEQ ID NO: 69, which is at least 80% identical to the claimed SEQ ID NO: 69 (see reference SEQ ID NO: 11, col. 7 lines 65-67 bridging col. 8, line 1, in particular). The term "or" in claims 1, 11 and 16 does not require the antibody to have the other sequence from the light chain. The reference antibody inherently also binds (cross-react) to human insulin-like growth factor I receptor IGF-IR given the level of sequence identity. Since the Patent Office does not have the facilities for examining and comparing the antibodies of the instant invention to those of the prior art, the burden is on applicant to show that the prior art antibody is different from the claimed antibody. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977). The reference also teaches chimeric antibody and humanized antibody comprising the varialbe region of the mouse monoclonal antibody and the light chain and heavy chain constant region derived from human, which is heterologous to the mouse (see col. 3, line 43-49, col. 6, lines 45-56, in particular). The reference antibody has a kappa light chain and a heavy chain of IgG2 (see col. 5, lines 12-20, in particular). The '841 patent teaches various hybridoma that are capable of secreting the reference antibodies (see claims of '841, in particular). Thus, the reference teachings anticipate the claimed invention.

25. Claims 1 and 15-16 are rejected under 35 U.S.C. 102(e) as being anticipated by US Pat No. US 6,300,064 B1 (filed August 19, 1996; PTO 892).

The '064 patent teaches an antibody that comprises a heavy chain sequence such as SEQ ID NO: 39 that is 81.9% identical to the claimed SEQ ID NO: 83 (see col. 3, lines 61-67, reference SEQ ID NO: 39, in particular). The term "or" in claim 16 does not require the antibody to have the other sequence from the light chain. The reference antibody inherently also binds (cross-react) to human insulin-like growth factor T receptor IGF-IR. Since the Patent Office does not have the facilities for examining and comparing the antibodies of the instant invention to

those of the prior art, the burden is on applicant to show that the prior art antibody is different from the claimed antibody. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977). Thus, the reference teachings anticipate the claimed invention.

26. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

27. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

28. Claims 1, 11-14 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,935,821 (issued Aug 1999; PTO 892) in view of US Pat No. 6,180,370B (filed June 1995; PTO 892).

The teachings of the '821 patent have been discussed supra. The '821 patent further teaches the reference antibody is useful for treating tumor (see abstract, in particular).

The invention in claim 12 differs from the teachings of the reference only in that the antibody or the binding fragment thereof is a chimeric antibody wherein the antibody comprises the light and heavy chain constant region derived from an antibody or a species heterologous to the mouse.

The invention in claim 13 differs from the teachings of the reference only in that the antibody or the binding fragment thereof is a chimeric antibody that comprises the light and heavy chain constant region derived from man.

The invention in claim 14 differs from the teachings of the reference only in that the chimeric antibody or the binding fragment thereof comprises the human kappa light and human heavy chain constant region from gamma-1.

The '370 patent teaches a method of producing chimeric antibodies (See column 55 lines 25-59; column 59, lines 65, in particular) and humanized antibodies (See column 44 line 33; column 68 lines 8-44, in particular). The '370 patent further teaches chimeric antibody whose light and heavy chain genes have been constructed, typically by genetic engineering from immunoglobulin variable and constant region genes belonging to different species such as the variable segments of the genes from a mouse monoclonal antibody may be joined to human constant such as human gamma 1 (IgG1) (see col. 11, lines 55-67, in particular), IgG2 or IgG4 (see col. 11, lines 5-20, in particular). The reference chimeric antibody retains the same affinity as the donor immunoglobulin to the antigen while the humanized immunoglobulins (antibodies) specifically reactive with strong affinity to a predetermined antigen and remain non-immunogenic in humans and yet be easily and economically produced in a manner suitable for therapeutic formulation and other uses (See column 2, lines 29-34, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to produce humanized or chimeric antibody that comprises the light and heavy chain constant region derived from man as taught by the '370 patent using the donor monoclonal antibody that comprises the light chain having a sequence such as SEQ ID NO: 66 that is 93.4% identical the claimed SEQ ID NO: 54 as taught by the '821 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated with an expectation of success to produce chimeric or humanized antibodies because the '370 patent teaches chimeric antibody has proven somewhat successful since chimeric antibody can loose the affinity for the antigen; humanized immunoglobulin (antibody) binds with strong affinity to a predetermined antigen and remain non-immunogenic in humans and yet be easily and economically produced in a manner suitable for therapeutic formulation and other uses (See column 2, lines 29-34, in particular). The '821 patent teaches the reference antibody is useful for treating tumor (see abstract, in particular).

29. Claims 1, 24-28, 31-37, 43-52 and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,891,996 (issued April 1999; PTO 892) as evidence by Rodeck et al (J Cell Biochem 35(4): 315-20, Dec 1987; PTO 892) in view of US Pat No. 6,342,219 B1 (filed April 28, 2000; PTO 892) and US Pat No 6,235,883 B1 (filed May 1997; PTO 892) or Ciardiello et al (Clinical Cancer Research 5: 909-916, April 1999; PTO 892).

The teachings of the '996 patent as evidence by Rodeck et al have been discussed supra.

The invention in claim 24 differs from the teachings of the references only in that the antibody or the binding fragment thereof is capable of binding to the human epidermal growth factor receptor and/or inhibiting the tyrosine kinase activity of said EGFR receptor.

The invention in claim 25 differs from the teachings of the references only in that the antibody or the binding fragment thereof is capable of binding to the human epidermal growth factor receptor and/or inhibiting the tyrosine kinase activity of said EGFR receptor wherein the antibody is a bispecific antibody.

The invention in claim 26 differs from the teachings of the references only in that the bispecific antibody or the binding fragment thereof is capable of binding to the human epidermal growth factor receptor and/or inhibiting the tyrosine kinase activity of said EGFR receptor wherein the antibody is bivalent or tetravalent.

The invention in claim 27 differs from the teachings of the references only in that the EGFR antibody is a fragment selected from the group Fv, Fab, F(ab')2, scFv, scFv or like pegylated fragment thereof.

The invention in claim 28 differs from the teachings of the references only in that the second antibody is an anti-EGFR antibody 225 or chimeric C225 or humanized C225.

The invention in claims 45-51 and 54 differs from the teachings of the references only in that a method of preparing for a preparation comprising the antibody.

The '219 patent also teaches a method of making various function fragment of any antibody such as Fab, Fab', single chain sFv, diabodies (see col. 73, lines 18-67 bridging col. 74, lines 1-5, in particular). The '219 patent also teaches conjugating any antibody to polyethylene glycol (PEG) increases the half-life of the reference antibody (see col. 74, lines 6-17, in particular).

The '883 patent teaches various antibodies such as monoclonal antibody C225 (see col. 23, line 10, in particular) and derivative of C225 such as humanized antibody (see col. 2, lines 32-35, in particular) or human antibody that binds specifically to human epidermal growth factor

receptor (EGF-r) (see entire document, col. 18-21, claims of '883 patent, in particular). The reference antibody inhibits the binding of human EGF to its receptor, the human epidermal growth factor receptor (see col. 31, lines 44-67, in particular). The '883 patent teaches various antibody fragments such as Fab, Fab', F(ab')2, Fv, single chain antibodies scFv, and bispecific antibody thereof (see col. 18, lines 3-6, in particular). Since the reference F(ab')2 fragment is bivalent, it is obviously that the reference bispecific antibody would be tetravalent. The reference teaches a composition comprising the reference anti-EGF receptor alone or in combination with a second compound such as cytotoxic/cytostatic or chemotherapeutic agent such as adriamycin, cisplatin, taxol or the like (spindle inhibitor), doxorubicin and the combination is useful for treating breast cancer (see col. 35, lines 1-17, col. 36, lines 50-67, col. 18, lines 55-60, in particular). The '883 patent also teaches the reference antibody is useful for diagnosis of illness such as cancer that is overexpressed IGF-IR and/or EGFR receptor and the antibody can be chemically labeled to an imaging agent for diagnosis (see col. 35, lines 30-49, col. 18, lines 25-46, in particular). The '883 patent further teaches a method of increasing the half-life of the reference antibody fragment such as substituting D-lysine in place of L-lysine to generate more stable peptide (see col. 17, lines 35-57, in particular). The '883 patent teaches the anti-EGF receptor antibody is efficacious in monotherapy in addition to combination with anti-neoplastic agent or chemotherapeutic agent such as cisplatin, topoetecan, doxorubicin, adriamycin, taxol, or the like (see col. 36, lines 60-63, in particular) with lower doses than the C225 antibody for treating tumor (see col. 21, lines 29-40, col. 35, lines 1-16, in particular). The '883 patent teaches a method of preparing the reference antibody alone or in combination with other anti-neoplastic agent for a medicament (see col. 16, lines 37-39, col. 19, lines 65 through col. 21, lines 15-22, in particular).

Ciardiello et al teach antibody such as anti-epidermal growth factor receptor monoclonal antibody C225 in combination with topotecan significantly additively inhibit the growth of human ovarian, breast cancer and colon cancer cell line (see entire document, abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the antibody that binds to human insulin-like growth factor I receptor as taught by the '996 patent with the antibody that binds to human epidermal growth factor receptor such as monoclonal C225 or humanized or human monoclonal antibody derived from m C225 alone or in combination with cytotoxic or cytostatic agent or chemotherapeutic

agent for treating cancer as taught by the '883 patent or Ciardiello et al. It would have been obvious to one of ordinary skill in the art at the time the invention was made to pegylated any antibody fragment to increase the half-life of the antibody fragment as taught by the '219 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '883 patent teaches the anti-EGF receptor antibody is efficacious in monotherapy in addition to combination with anti-neoplastic agent with lower doses than the C225 antibody (see col. 21, lines 29-40, in particular). The '996 patent teaches the reference antibody that binds to human insulin-like growth factor 1 receptor is useful for treating tumor and/or diagnosis of tumor (see col. 4, lines 4-12, in particular). Ciardiello et al teach antibody such as anti-epidermal growth factor receptor monoclonal antibody C225 in combination with topotecan significantly additively inhibit the growth of human ovarian, breast cancer and colon cancer cell line (see entire document, abstract, in particular). In re Kerkhoven, 205USPQ 1069 (CCPA 1980), recognized that "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose ... [T]he idea of combining them flows logically from their having being individually taught in the prior art" (see MPEP 2144.06). It is within the purview of one ordinary skill in the pharmaceutical to administer the composition simultaneously, separately or sequentially.

30. Claims 1, 29-30, 36-39, 43 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,891,996 (issued April 1999; PTO 892) as evidence by Rodeck et al (J Cell Biochem 35(4): 315-20, Dec 1987; PTO 892) in view of US Pat No. 6,342,219 B1 (filed April 28, 2000; PTO 892).

The combined teachings of the '996 patent as evidence by Rodeck et al have been discussed supra. The '966 patent further teaches antibodies such as humanized, chimeric and monoclonal antibodies against human EGF receptor are useful for treating tumor (see col. 4, lines 4-10, in particular).

The invention in claim 29 differs from the teachings of the references only in that the antibody is a functional fragment thereof.

The invention in claim 38 differs from the teachings of the references only in that the composition wherein the cytotoxic/cytostatic agent is coupled chemically to at least one of the antibody or binding fragment thereof in the composition for simultaneous use.

The invention in claim 39 differs from the teachings of the references only in that the composition wherein the cytotoxic/cytostatic agent is coupled chemically to at least one of the antibody or binding fragment thereof wherein the agent is selected from the group consisting of vinblastine, deoxyvinblastine, vincristine, vindesine, vinorelbine, vinepidine, vinfosiltine, vinzolidine and vinfunine.

The invention in claim 43 differs from the teachings of the references only in that the composition wherein at least one of the antibody or functional fragment is conjugated with a cell toxin.

The invention in claim 53 differs from the teachings of the references only in that a kit comprising an antibody or one of its functional fragments, optionally the reagents for the formation of the medium favorable to the immunological reaction and optionally the reagents allowing the demonstration of the IGF-IR antibody and/or EGFR antibody complexes produced by the immunological reaction.

The '219 patent teaches preparation of immunoconjugates and immunotoxins is generally well known in the art (see col. 30, lines 6-20, in particular). The '219 patent teaches anti-VEGF antibody or binding fragment thereof conjugated to various cytotoxic/cytostatic agent such as vinca alkaloids such as vinblastine, vincristine, vindescine and derivative thereof (see col. 28, lines 29-60, col. 29, lines 38-40, in particular) or toxin such as ricin A chain (see col. 29, lines 5-11, in particular) to be used simultaneous for targeting therapeutic agent to the tumor (see col. 35, lines 17-32, in particular). The '219 patent teaches chemically linking various cytotoxic/cytostatic agent or toxin with antibody is useful for targeting the cytotoxic/cytostatic agent or toxin to the tumor or cell of interest and any potential side-effects from the cytotoxin based therapy may be minimized (see col. 76, lines 1-20, in particular). The '219 patent also teaches a method of making various function fragment of any antibody such as Fab, Fab', single chain sFv, diabodies (see col. 73, lines 18-67 bridging col. 74, lines 1-5, in particular). The '219 patent also teaches conjugating the reference antibody to PEG to increase the half-life of any antibody (see col. 74, lines 6-17, in particular). The '219 patent further teaches a kit comprising the reference antibody for detection or diagnosing VEGF immunocomplex (see col. 127, line 35 bridging col. 128, lines 1-67, in a particular). The reference kit further comprises all the

necessary reagents for the formation of the medium favorable to the immunological reaction (See col. 130, lines 40-67 bridging col. 131, lines 1-38, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the anti-VEGF antibody in the immunoconjugate of the composition as taught by the '219 patent for the antibodies such as humanized, chimeric and monoclonal antibodies against human EGF receptor as taught by the '966 patent for a composition comprising antibody that binds to human insulin-like growth factor I receptor coupled chemically to vinblastine, vincristine, vindescine or derivative thereof or toxin. It would have been obvious to one of ordinary skill in the art at the time the invention was made to put the mAb as taught by the '996 patent in a kit as taught by the '219 patent because a kit will allow for ease of use for the practitioner since all the necessary reagents, standard and instructions for use are included in a kit as taught by '219 (See col. 130, lines 40-67 bridging col. 131, lines 1-38, in particular). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because chemically linking various cytotoxic/cytostatic agent or toxin with antibody is useful for targeting the cytotoxic/cytostatic agent or toxin to the tumor or cell of interest and any potential side-effects from the cytotoxin based therapy may be minimized as taught by the '219 patent (see col. 76, lines 1-20, in particular). A kit containing the reference antibody and appropriate reagents will allow for ease of use for the practitioner since all the necessary reagents, standard and instructions for use are included in a kit as taught by '219 (See col. 130, lines 40-67 bridging col. 131, lines 1-38, in particular). The '966 patent teaches antibodies such as humanized, chimeric and monoclonal antibodies against human EGF receptor are useful for treating tumor (see col. 4, lines 4-10, in particular).

31. Claims 1, 30 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,891,996 (issued April 1999; PTO 892) as evidence by Rodeck et al (J Cell Biochem 35(4): 315-20, Dec 1987; PTO 892) in view of Traxler et al (J Pharm Belg 52(2): 88-96, 1997; PTO 892).

The combined teachings of the '996 patent as evidence by Rodeck et al and the '883 patent have been discussed supra. The '966 patent further teaches antibodies such as humanized,

chimeric and monoclonal antibodies against human EGF receptor are useful for treating tumor (see col. 4, lines 4-10, in particular).

The invention in claim 36 differs from the combined teachings of the references only in that the composition wherein the inhibitor of tyrosine kinase activity for IGF-I and/or EGF is a natural derived agent such as dianilino-phthalimide, pyrazolo-or pyrrolopyridopyrimidines or quinazilines.

Traxler et al teach various tyrosine kinase inhibitors that are specific to EGF receptor tyrosine kinase such as dianilinophthalimide (CGP 52411) or CGP53353 or phenylaminoquinazoline (PD153035) or phenylamino-pyrido-pyrimidines (see entire document, page 89, page 91, col. 2, in particular). Traxler et al further teach inhibitors of the EGF-R protein tyrosine kinase could have great therapeutic potential in the treatment of malignant (anti-tumor) and nonmalignant disease (see page 88, col. 2, page 91, page 92, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the antibody that binds to human insulin-like growth factor I receptor as taught by the '996 patent with the various EGF receptor specific tyrosin kinase inhibitor such as dianilinophthalimide (CGP 52411) or CGP53353 or phenylaminoquinazoline (PD153035) or phenylamino-pyrido-pyrimidines as taught by Traxler et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because inhibitors of the EGF-R protein tyrosine kinase could have great therapeutic potential in the treatment of malignant (anti-tumor) and nonmalignant disease as taught by Trexler et al (see page 88, col. 2, page 91, page 92, in particular). The '966 patent teaches antibodies such as humanized, chimeric and monoclonal antibodies against human EGF receptor are useful for treating tumor (see col. 4, lines 4-10, in particular). In re Kerkhoven, 205USPQ 1069 (CCPA 1980), recognized that "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose ... [T]he idea of combining them flows logically from their having being individually taught in the prior art" (see MPEP 2144.06).

32. Claims 1, 30-32 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,891,996 (issued April 1999; PTO 892) as evidence by Rodeck et al (J Cell Biochem 35(4): 315-20, Dec 1987; PTO 892) in view of US Pat No 6,235,883 B1 (filed May 1997; PTO 892) and Traxler et al (J Pharm Belg 52(2): 88-96, 1997; PTO 892).

The combined teachings of the '996 patent as evidence by Rodeck et al have been discussed supra.

The invention in claim 40 differs from the combined teachings of the references only in that the composition comprising an antibody or binding fragment thereof that binds to human insulin-like growth factor I receptor (IGF-IR), an anti-EGFR antibody or binding fragment thereof and an inhibitor of tyrosine kinase activity for IGF-I and/or EGF wherein the inhibitor is a natural derived agents such as dianilino-phthalimide, pyrazolo-or pyrrolopyridopyrimidines or quinazilines.

The '883 patent teaches various antibodies such as monoclonal antibody C225 (see col. 23, line 10, in particular) and derivative of C225 such as humanized antibody (see col. 2, lines 32-35, in particular) or human antibody that binds specifically to human epidermal growth factor receptor (EGF-r) (see entire document, col. 18-21, claims of '883 patent, in particular). The reference antibody inhibits the binding of human EGF to its receptor, the human epidermal growth factor receptor (see col. 31, lines 44-67, in particular). The '883 patent teaches various antibody fragments such as Fab, Fab', F(ab')2, Fv, single chain antibodies scFv, and bispecific antibody thereof (see col. 18, lines 3-6, in particular). Since the reference F(ab')2 fragment is bivalent, it is obviously that the reference bispecific antibody would be tetravalent. The reference teaches a composition comprising the reference anti-EGF receptor alone or in combination with a second compound such as cytotoxic/cytostatic or chemotherapeutic agent such as adriamycin, cisplantin, taxol or the like (spindle inhibitor), doxorubicin and the combination is useful for treating breast cancer (see col. 35, lines 1-17, col. 36, lines 50-67, col. 18, lines 55-60, in particular). The '883 patent also teaches the reference antibody is useful for diagnosis of illness such as cancer that is overexpressed IGF-IR and/or EGFR receptor and the antibody can be chemically labeled to an imaging agent for diagnosis (see col. 35, lines 30-49, col. 18, lines 25-46, in particular). The '883 patent further teaches a method of increasing the half-life of the reference antibody fragment such as substituting D-lysine in place of L-lysine to generate more stable peptide (see col. 17, lines 35-57, in particular). The '883 patent teaches the anti-EGF receptor antibody is efficacious in monotherapy in addition to combination with anti-neoplastic

agent or chemotherapeutic agent such as cisplantin, topoetecan, doxorubicin, adriamycin, taxol, or the like (see col. 36, lines 60-63, in particular) with lower doses than the C225 antibody for treating tumor (see col. 21, lines 29-40, col. 35, lines 1-16, in particular). The '883 patent teaches a method of preparing the reference antibody alone or in combination with other anti-neoplastic agent for a medicament (see col. 16, lines 37-39, col. 19, lines 65 through col. 21, lines 15-22, in particular).

Traxler et al teach various tyrosine kinase inhibitors that are specific to EGF receptor tyrosine kinase such as dianilinophthalimide (CGP 52411) or CGP53353 or phenylaminoquinazoline (PD153035) or phenylamino-pyrido-pyrimidines (see entire document, page 89, page 91, col. 2, in particular). Traxler et al further teach inhibitors of the EGF-R protein tyrosine kinase could have great therapeutic potential in the treatment of malignant (anti-tumor) and nonmalignant disease (see page 88, col. 2, page 91, page 92, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the anti-EGFR antibody or binding fragment thereof as taught by the '883 patent, the anti-human insulin-like growth factor I receptor or binding fragment thereof as taught by the '996 patent with the various tyrosine kinase receptor inhibitor such as dianilinophthalimide (CGP 52411) or CGP53353 or phenylaminoquinazoline (PD153035) or phenylamino-pyrido-pyrimidines as taught by Traxler et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because inhibitors of the EGF-R protein tyrosine kinase could have great therapeutic potential in the treatment of malignant (anti-tumor) and nonmalignant disease as taught by Trexler et al (see page 88, col. 2, page 91, page 92, in particular). The '883 patent teaches the anti-EGF receptor antibody is efficacious in monotherapy in addition to combination with anti-neoplastic agent or chemotherapeutic agent such as cisplatin, topoetecan, doxorubicin, adriamycin, taxol, or the like (see col. 36, lines 60-63, in particular) with lower doses than the C225 antibody for treating tumor (see col. 21, lines 29-40, col. 35, lines 1-16, in particular). The '966 patent teaches antibodies such as humanized, chimeric and monoclonal antibodies against human EGF receptor are useful for treating tumor (see col. 4, lines 4-10, in particular). In re Kerkhoven, 205USPQ 1069 (CCPA 1980), recognized that "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to

be used for the very same purpose ... [T]he idea of combining them flows logically from their having being individually taught in the prior art" (see MPEP 2144.06).

33. Claims 1, 30, 41 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,891,996 (issued April 1999; PTO 892) as evidence by Rodeck et al (J Cell Biochem 35(4): 315-20, Dec 1987; PTO 892) in view of US Pat No 6,949,245 B1 (filed June 25, 2000; PTO 892) or Baselga et al (Semin Oncol 26(4 suppl 12): 78-73, August 1999, abstract only; PTO 892).

The combined teachings of the '996 patent as evidence by Rodeck et al have been discussed supra.

The invention in claim 41 differs from the teachings of the references only in that the composition further comprises another antibody compound directed against the extracellular domain of the HER2/neu receptor as a combination product for simultaneous, separate or sequential use intended for the treatment of cancer.

The invention in claim 42 differs from the teachings of the references only in that the composition further comprises another antibody compound directed against the extracellular domain of the HER2/neu receptor wherein the antibody is Trastuzumab or its functional fragment thereof.

The '245 patent teaches various antibodies such as human Mab 4D5, recombinant human Mab HER2 or Herceptin such as 2C4 and binding fragment thereof that bind specifically to HER2/neu receptor and are useful for treating ErbB2 overexpressing metastatic breast cancer (see entire document, col. 2, lines 42-51, col. 13, lines 66-67 bridging col. 14, in particular).

Baselga et al teach trastuzumab is a recombinant humanized monoclonal antibody with high affinity to the HER2 protein and this antibody inhibits the growth of metastatic breast cancer cells overexpressing HER2 (see abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the antibody that binds specifically to human EGF receptor and cross-react with human insulin-like growth factor I receptor as taught by the '996 patent with the human Mab 4D5 or recombinant human Mab HER2 or binding fragment thereof as taught by the '245 patent or the trastuzumab humanized monoclonal antibody or binding fragment thereof that binds to HER2 with high affinity as taught by Baselga et al for treatment of cancer. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '245 patent teaches the antibodies to HER2/neu receptor in combination with other compound is useful for treating cancer overexpressing HER2 (see claims of the '245 patent, in particular). Baselga et al teach trastuzumab is a recombinant humanized monoclonal antibody with high affinity to the HER2 protein and this antibody inhibits the growth of metastatic breast cancer cells overexpressing HER2 (see entire document, abstract, in particular). The '996 patent teaches the reference antibody that binds to human insulin-like growth factor 1 receptor is useful for treating tumor and/or diagnosis of tumor (see col. 4, lines 4-12, in particular). In re Kerkhoven, 205USPQ 1069 (CCPA 1980), recognized that "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose ... [T]he idea of combining them flows logically from their having being individually taught in the prior art" (see MPEP 2144.06).

34. Claims 2-3, 9-10, and 17 are free of prior art.

35. No claim is allowed.

36. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

37. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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1/20/06